Cushing's syndrome caused by nodular adrenal hyperplasia in children with McCune-Albright syndrome

Jeremy M. W. Kirk, MD, Caroline E. Brain, MD, Dennis J. Carson, MB,BCh, John C. Hyde, MB,BCh, and David B. Grant, MD†

McCune-Albright syndrome consists of fibrous dysplasia of bone, café-au-lait skin pigmentation, and endocrine dysfunction (usually precocious puberty). Other endocrine abnormalities occur in a minority of patients, and of these, Cushing's syndrome is the least often recognized. We present 5 children (4 girls) with features of McCune-Albright syndrome who had Cushing's syndrome in the infantile period (<6 months). In 2 children spontaneous resolution occurred, but the remaining 3 required bilateral adrenalectomy. In addition, all 4 girls have experienced precocious puberty, and 3 children demonstrated radiologic evidence of nephrocalcinosis. Understanding of the underlying defect causing McCune-Albright syndrome emphasizes the importance of searching for other endocrine dysfunction in these children. (J Pediatr 1999;134:789-92)

In 1937 Albright et al[1] described 5 patients with bony lesions, skin pigmentation, and in the female patients, endocrine dysfunction associated with precocious puberty. Since that time, the spectrum of endocrine abnormalities has expanded to include disorders of the thyroid, parathyroid, pituitary, and adrenal glands and the renal tubule.[2] Of the endocrinopathies, Cushing's syndrome is rarely described, with only 6 previous case reports in the literature. We now describe an additional 5 infants with McCune-Albright syndrome who presented soon after birth with Cushing's syndrome.

From the Hospital for Sick Children, London, United Kingdom; Queen's University of Belfast, Belfast, United Kingdom; and The Lister Hospital, Stevenage, United Kingdom.

†Dr Grant died in September 1997.

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Reprint requests: Jeremy M. W. Kirk, Department of Endocrinology, Birmingham Children's Hospital, Birmingham B4 6NH, United Kingdom.

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CASE REPORTS

(See Also Tables I and II)

Patient 1 was born at 37 weeks' gestation weighing 1.68 kg. At 7 weeks of age she experienced vomiting and abdominal distension. Laparotomy revealed multi-loculated ovarian cysts, which were resected. She had a cushingoid appearance, hypertrichosis, café-au-lait patches on the face and back, bilateral abdominal masses, and prominent labia minora with clitoromegaly. Investigation showed elevated plasma cortisol levels with no suppression after administration of dexamethasone, low plasma corticotropin levels, and excess urinary excretion of cortisol and androgens. Abnormal bone texture was seen on skeletal survey. Abdominal ultrasonography showed bilateral ovarian cysts and nephrocalcinosis. Bilateral adrenalectomy at 3 months revealed nodular hyperplasia. Irregular vaginal bleeding occurred in association with breast development, and treatment with cyproterone acetate was started at 11 months of age. Thyrotoxicosis subsequently developed, and she required therapy with carbimazole. A number of pathologic fractures of both femora through polyostotic lesions were found, and in addition, she has marked spinal deformity. She has severe feeding problems and both developmental and physical delay.

Patient 2 weighed 1.96 kg at term. At 5 months of age, she presented with feeding difficulties, developmental delay, and respiratory distress. Examination revealed café-au-lait skin pigmentation and a cushingoid appearance. Investigation showed elevated plasma cortisol levels and no suppression after dexamethasone administration; urine steroid metabolite levels were also raised. Skeletal survey demonstrated polyostotic fibrous dysplasia. Abdominal ultrasonography showed bilateral ovarian cysts and nephrocalcinosis. Treatment with metyrapone was unsuccessful, and bilateral adrenalectomy was performed at 7 months of age; both glands showed nodular hyperplasia. At the age of 22 months she had irregular vaginal bleeding and early breast development. She has also experienced thyrotoxicosis, requiring treatment with carbimazole.

Table I. Clinical details of patients

Sex	Age at time of Cushingoid appearance	Adrenal-ectomy	Sexual precocity	Café-au-lait pigmentation	Fibrous dysplasia
Present cases					
F	3 mo	3 mo	2 mo, Ovarian cysts	3 mo	3 mo
F	5 mo	5 mo	5 mo, Ovarian cysts	5 mo	5 mo
F	3 mo	—	21 mo, Vaginal bleeding	6 wk	3 mo
M	4 mo	5 mo	—	Birth	4 mo
F	3 mo	—	4 y, Breast enlargement	7 mo	3 y
Previously reported cases					
F	1 mo	4 mo	4 y, Vaginal bleeding	1 y	4 y
M	17 y	(L) 17 y	6 y, Enlarged testes and pubic hair	Birth	3 y
F	Neonatal	8 mo	5 mo, Vaginal bleeding and breast development	Birth	6 mo
M	3 y	4 y	—	3 y	2 y
F	1 mo	—	—	1 mo	1 mo
M	Neonatal	6 wk	—	—	Infancy

GH, Growth hormone.

Table II. Endocrine details of present patients

Patient No.	Baseline 8 AM Cortisol (μg/dL)	Midnight cortisol (μg/dL)	Cortico-tropin (ng/L)	Urine free cortisol (μg/d)	Low-dose dexamethasone 8 AM Cortisol (μg/dL)	Midnight cortisol (μg/dL)	Urine free cortisol (μg/d)	High-dose dexamethasone 8 AM Cortisol (μg/dL)	Midnight cortisol (μg/dL)	Urine free cortisol (μg/d)
1	53.0	51.4	<7	373	40.0	38.4	—	>58.0	56.7	—
2	40.4	51.4	—	—	37.5	—	—	37.6	—	—
3	9.6	8.5	10	118	—	—	217	—	—	—
4	19.2	19.6	<10	122	36.6	36.2	122	25.4	25.4	59
5	11.4	14.1	<10	24.0	16.7	17.4	17	22.5	23.6	70

Patient 3 was born at 41 weeks' gestation weighing 2.5 kg. At 6 weeks of age she was noted to be hypotonic and to have pigmentation over the left side of the face. Renal ultrasonography showed bilateral nephrocalcinosis, and echocardiography revealed hypertrophic cardiomyopathy. A skeletal survey showed radiolucent and sclerotic areas, consistent with fibrous dysplasia. She was noted to have a cushingoid appearance, and serum cortisol levels showed loss of diurnal variation and failure of suppression with both low- and high-dose dexamethasone. By 6 months of age, however, there had been clinical resolution of her Cushing's syndrome without treatment, although she continued to demonstrate lack of diurnal variation in cortisol production and lack of suppression with dexamethasone. At 18 months of age she had vaginal bleeding.

Patient 4, a male infant and the second of twins, was born at 39 weeks' gestation by normal delivery weighing 2.92 kg. Despite feeding well, weight gain in the first 3 months of life was poor, and in-

Fibrous dysplasia	Other endocrinopathy/ renal problems	Reference
3 mo	Thyrotoxicosis, nephrocalcinosis	
5 mo	Thyrotoxicosis, nephrocalcinosis	
3 mo	Nephrocalcinosis	
4 mo	—	
3 y	Cystic right ovary	
4 y	—	3
3 y	Pituitary adenoma, nodular goiter, Leydig cell hyperplasia	4
6 mo	Cystic left ovary	5
2 y	Thyrotoxicosis, GH hypersecretion	6
1 mo	Thyrotoxicosis, nephrocalcinosis, cystic right ovary	7
Infancy	—	8

creasing café-au-lait pigmentation over the cheeks, neck, and back was noted. At 4 months of age, he appeared cushingoid and was hypertensive (blood pressure, 120/80 mm Hg). Serum cortisol production was increased with loss of diurnal variation, and corticotropin levels were persistently low. There was failure of suppression with low- and high-dose dexamethasone. Radiologic examination of the femora showed cystic changes consistent with polyostotic fibrous dysplasia. Bilateral adrenalectomy was performed at 5 months of age, and histologic examination showed bilateral nodular hyperplasia, but even with adequate steroid replacement therapy, he did not show catch-up growth. At 8 months of age, after a short illness, he suddenly collapsed and died.

Patient 5 was born by normal delivery at term weighing 2.89 kg. At 3 months of age she had a cushingoid appearance with a blood pressure of 120/86 mm Hg. Faint areas of irregular pigmentation were present over the right thoracolumbar area. Both serum and urine cortisol levels showed a paradoxical rise after administration of high-dose dexamethasone, and the basal corticotropin level was normal. Computed tomographic scan of the abdomen demonstrated enlarged adrenal glands. She received no treatment, and the cushingoid appearance gradually improved, although pigmentation became more pronounced. At 3 years of age a skeletal survey revealed changes of fibrous dysplasia in the left tibia, metacarpals, and phalanges. At 4 years of age early breast development was noted, and ultrasonographic examination showed cystic changes in the right ovary and enlargement of the uterus. There was some regression of breast development, although menarche occurred when she was almost 6 years old.

RESULTS

(Table I)

All children were diagnosed as having McCune-Albright syndrome on the basis of café-au-lait pigmentation and bony changes of polyostotic fibrous dysplasia (although patient 1 had initially presented with ovarian cysts requiring laparotomy). Café-au-lait skin pigmentation was described in only one child (patient 4) at birth; in one child (patient 5) evidence of fibrous dysplasia was not present until 3 years of age. Patient 3 also had transient hypercalcemia (serum calcium level between 12 and 12.8 mg/dL) with hypercalciuria, but with normal parathormone and vitamin D levels.

Endocrine assessment of the patients is shown in Table II. The diagnosis of adrenal-dependent Cushing's syndrome was made in all 5 children on the basis of loss of diurnal variation in cortisol production and failure of suppression after administration of low- and high-dose dexamethasone.

Two children (patients 3 and 5) experienced spontaneous clinical resolution of Cushing's syndrome, but the remaining 3 required bilateral adrenalectomy between 3 and 5 months of age. Histologic examination of the adrenal glands revealed nodular hyperplasia in all glands.

DISCUSSION

Five patients with McCune-Albright syndrome with associated Cushing's syndrome have been well documented,[3-7] with an additional brief report of another patient.[8] Although none of these patients showed spontaneous resolution of Cushing's syndrome, there are reports of autopsy findings describing nodular adrenal hyperplasia in McCune-Albright syndrome not associated with clinically apparent Cushing's syndrome.[9-10]

All 5 patients described in this report (and both children from previous reports who were tested) showed autonomous cortisol secretion, which was not suppressed by high-dose dexamethasone. The adrenal histology demonstrated nodular hyperplasia in all but one gland,[4] which demonstrated an adenoma. This patient was also unusual both in the age at presentation (17 years) and severity of disease, with other endocrinopathies including pituitary adenoma, nodular goiter, and Leydig cell hyperplasia causing precocious puberty (in contrast to the other 3 male patients described).

Because endocrine hyperactivity appears to be autonomous, this may be due to affected tissues showing activation of the signal transduction pathway generating cyclic adenosine monophosphate. This hypothesis has been confirmed by demonstration of a mutation in the alpha subunit of the G_s protein in virtually all affected tissues in patients with McCune-Albright syndrome, including the adrenal gland.[11]

In addition, 3 children (patients 1, 2, and 3) had nephrocalcinosis.[12] Although high serum calcium levels and hypercalciuria were documented in one, none of the children demonstrated evidence of hyperparathyroidism. It

is postulated that the hypercalcemia and hypercalciuria are secondary to the effects of cortisol on bone turnover.

In summary, Cushing's syndrome may be an early feature of McCune-Albright syndrome and usually presents in infancy. Skin and bony changes are often present, but their late appearance may delay the diagnosis. Adrenal disease is frequently associated with sexual precocity, and both disorders represent autonomous activity of the adrenal glands and gonads. Mild disease may not require immediate intervention, because spontaneous resolution may occur.

REFERENCES

1. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. N Engl J Med 1937;216:727-46.
2. Danon M, Crawford JD. The McCune-Albright syndrome. Ergebnisse der Inneren Medizin und Kinderheilkunde 1987;55:81-115.
3. Aarskog D, Tveteraas E. McCune-Albright syndrome following adrenalectomy for Cushing's syndrome in infancy. J Pediatr 1968;73:89-96.
4. Benjamin DR, McRoberts JW. Polyostotic fibrous dysplasia associated with Cushing syndrome. Arch Pathol 1973;96:175-8.
5. Danon M, Roboy SJ, Kim S, Scully R, Crawford JD. Cushing syndrome, sexual precocity and polyostotic fibrous dysplasia (Albright syndrome) in infancy. J Pediatr 1975;87:917-21.
6. Mauras N, Blizzard RM. The McCune-Albright syndrome. Acta Endocrinol (Copenh) 1986;279(suppl): 207-17.
7. Yoshimoto M, Nakayama M, Baba T, Uehara Y, Niikawa N, Ito M, et al. A case of neonatal McCune-Albright syndrome with Cushing syndrome and hyperthyroidism. Acta Paediatr Scand 1991;80:984-7.
8. Post EM, Consenstein L, Hitch D, Oliphant M, Dracker R, Richman RA. Congenital Cushing syndrome with polyostotic fibrous dysplasia (PFD) [abstract]. Pediatr Res 1983;17:169A.
9. MacMahon HE. Albright's syndrome—thirty years later (polyostotic fibrous dysplasia). Pathol Ann 1971;6: 81-146.
10. Joisy SK, Morrow LB. McCune Albright syndrome associated with a functioning pituitary chromophobe adenoma. J Pediatr 1975;87:73-5.
11. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 1991;325: 1688-95.
12. Kessel D, Hall CM, Shaw DG. Two unusual cases of nephrocalcinosis in infancy. Pediatr Radiol 1992;22:470-1.